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Editorial Comment

Multivessel Balloon Angioplasty Should Be Abandoned in Diabetic Patients!*

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Revascularization decision. When we as clinicians sit with a patient and their family to advise them about revascularization, an enormous professional and ethical obligation is placed on our shoulders. Patients literally and figuratively place their lives in our hands. Often at the end of a long complex discussion about outcomes, risks, benefits and costs, a patient will look straight into your soul and say, "I'll do whatever you say." Or, equally pointedly, "If I was your (mother/father/brother), what would you advise?" Experienced clinicians recognize that the choice of revascularization procedures is unique to each patient. A myriad of social, economic, medical and, finally, technical factors enter into our synthesis for an ultimate recommendation. Because patients and society have placed this enormous responsibility on us, it is imperative that we become well armed with as much information as possible to assist our patients in making an informed decision that is right for them. This information must include an in-depth knowledge of the patient's personal expectations and family needs and resources. Of course, a detailed knowledge about the disease process and an estimate of individual long-term prognosis are necessary. It is also necessary to include detailed, objective technical proficiency data about the surgical or interventional program to which the patient is referred. Finally, we must ensure that self-referral bias does not enter this equation.

After discussing personal needs and expectations, patients are intently interested in technical details. Will it hurt? How long will I be in the hospital? How long will it take to recover? When can I return to work? These patient comfort questions have tended to favor balloon angioplasty over bypass surgery in the past. An important, previously unanswerable, question was, "Which treatment will allow me to live longer?"

To this end, Weintraub et al. (1) in this issue of the Journal attempt to provide long-term outcome information for diabetic patients with multivessel disease undergoing revascularization at Emory University Hospital from 1981 to 1994. Because diabetic patients comprise 20% to 30% of interventional practices, the unique characteristics of this patient population are critically important to understand. The authors conclude that diabetic patients treated with angioplasty had less extensive disease, slightly better ventricular function and no difference in unadjusted long-term survival. Although at first glance this analysis is reassuring, a more detailed analysis suggests that when risk adjustment for baseline variables occurs, diabetic patients fare better with bypass surgery than with angioplasty. Given these unexpected findings, should a moratorium be placed on percutaneous intervention in diabetic patients?

Diabetes mellitus is a potent risk factor for the development of coronary artery disease and independently worsens long-term prognosis for medically treated patients (2–4). The mechanism for hyperglycemia and hyperinsulinemia to accelerate development and progression of coronary artery disease is multifactorial. Endothelial dysfunction, enhanced platelet activation, enhanced prothrombotic activity and enhanced growth factor production can all contribute to rapid disease progression. These same factors may explain the proclivity for restenosis that is apparent after coronary angioplasty.

Outcome after bypass surgery. Before rushing all our patients off to bypass surgery, it must be understood that diabetes also adversely affects short- and long-term outcome after coronary bypass. In the Emory experience, the in-hospital mortality rate was 5% in bypass group patients compared with 0.36% in coronary angioplasty group patients. In the Bypass Angioplasty Revascularization Investigation (BARI) (5), the mortality rate was double (1.2% vs. 0.6%) for surgically treated patients with diabetes. Herlitz et al. (6) has demonstrated that initial and 2-year survival were significantly worse for diabetic patients operated on in Goteborg, Sweden. Diabetic patients have more diffuse atherosclerosis, making grafting less successful. Patients with adult-onset diabetes often tend to be obese. Diabetes affects wound healing and predisposes to postoperative infections. All these factors make surgeons cautious about operating on diabetic patients. Finally, the BARI study itself has again demonstrated that surgically treated diabetic patients have a worse 5-year survival probability than nondiabetic patients (80.6% vs. 91.4%).

Outcome after angioplasty. When balloon angioplasty was first developed, patient selection was confined to patients with single-vessel disease; isolated, concentric, noncalcified lesions; and normal ventricles. In these types of patients, prognosis was excellent, irrespective of therapy. Now that percutaneous intervention has broadened to include complex diffuse disease, multivessel disease, unstable angina and acute myocardial infarction, it is likely that subgroups with an improved or worsened prognosis may be identified. One such subgroup is insulin-treated diabetic patients. The National Heart, Lung, and Blood Institute (NHLBI)-I registry (7) found no difference in hospital outcome for diabetic patients. As more complex disease was tackled in the NHLBI-II (8) registry, diabetic patients had a worse in-hospital mortality rate (3.2% vs. 0.5%). More recently, the Emory experience has found that as tech-

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Abbreviations and Acronyms

BARI = Bypass Angioplasty Revascularization Investigation
NHLBI = National Heart, Lung, and Blood Institute

nique has improved, mortality is the same for patients with and without diabetes (<0.4%). At the present time, diabetes does not appear to worsen the immediate outcome for percutaneous coronary intervention.

Unfortunately, the long-term outcome does appear to be dramatically impacted. Because immediate outcome and major cardiac events are not elevated in diabetic patients, the adverse outcome must be related to disease progression and restenosis. The hyperglycemia and hyperinsulinemia that promote atherosclerosis progression also dramatically enhance restenosis. Hyperglycemia causes endothelial dysfunction by decreasing endothelium-derived relaxing factor production (9), increasing free radical formation (10) and decreasing prostocyclin production (11). At the same time, platelet hyperaggregability occurs. Enhanced thromboxane A_2 production (12) and increased Factor VII (13) and anti-thrombin III (14) production occur. These factors predispose vessels to coronary thrombosis. Van Belle et al. (15) have in fact demonstrated that late vessel occlusion occurs in 14% of diabetic versus 3% of nondiabetic patients treated with coronary angioplasty.

Although hyperglycemia promotes thrombosis, hyperinsulinemia is a potent mitogen for restenosis. Platelet-derived growth factor and insulin-like growth factor are elevated in diabetic patients and may promote smooth muscle cell transformation (16). Strict glycemic control may downregulate these prothrombotic and prorestenotic factors. Aronson et al. (17) have elegantly made the argument for a clinical trial of strict diabetic control in diabetic patients treated with angioplasty.

In the context of the known predilection for thrombosis and restenosis to occur in diabetic patients, the worsened long-term outcome for these patients is understandable. Holmes et al. (7) first reported that diabetic patients had a higher restenosis rate in the NHLBI-I registry (47% vs. 32%). Kip et al. (8) found major adverse consequences in diabetic patients in the NHLBI-II registry. They reported a 9-year mortality rate of 35.9% versus 17.9% and 9-year rates of myocardial infarction of 29% versus 18% for diabetic and nondiabetic patients, respectively. Stein et al. (18) similarly reported on the Emory experience and found a 36% versus 53% 5-year event-free survival rate for diabetic versus nondiabetic patients. In fact, the 5-year survival rate was significantly lower (88% vs. 93%, $p < 0.0001$) for diabetic patients. Finally, the BARI trial found that the 5-year survival rate after diabetes was lower (65.5% vs. 91.4%) for diabetic patients.

The high rate of restenosis and late occlusion is difficult to diagnose because of the known tendency for diabetic patients to present with silent ischemia. Because ventricular function, extent of disease and angioplasty results are the same in diabetic patients, the worse long-term survival can only be explained by late coronary occlusion causing fatal myocardial infarction or restenosis causing ischemia and predisposing to lethal arrhythmias.

Outcome after stent implantation. The advent of widespread coronary stenting has dramatically altered interventional cardiology practice. Whether the improved restenosis rates reported in the randomized trials also occur in diabetic patients remains controversial. Van Belle et al. (15) have carefully studied two large groups of patients treated with coronary angioplasty or single-stent implantation. They reported similar rates of restenosis and late loss in diabetic and nondiabetic patients undergoing stenting.

Conversely, Kornowski et al. (19) have reported similar elevated rates of fibrointimal hyperplasia in diabetic patients with stenting. This finding has translated into enhanced rates of target lesion revascularization at the Washington Heart Center. Tilli et al. (20) reported on the William Beaumont Hospital experience and also found higher rates of target lesion revascularization in diabetic patients. Finally, Carozza et al. (21) demonstrated enhanced late loss in diabetic stent-treated patients at Beth Israel Hospital. All these studies are retrospective and have multiple confounding variables, such as different anticoagulation regimes, different stent deployment techniques and different numbers of stents deployed. Suffice it to say that the same propensity for restenosis that occurs after balloon angioplasty may still be a problem after stent implantation.

Call to arms. Are these data sufficiently compelling to warrant abandonment of balloon angioplasty in diabetic patients? Given the disturbing mortality results from the BARI trial and the present report by Weintraub et al. (1), and given the exorbitant rates of restenosis and the major events reported by Van Belle et al. (15) and Stein et al. (18), I believe that this therapy, as practiced (circa 1990), should be abandoned. After all, balloon aortic valvuloplasty was abandoned as an alternative to valve replacement when restenosis rates of 60% to 80% were reported (22). Multilesion balloon angioplasty in treated diabetic patients approaches these numbers. However, we may not do our patients justice by subjecting them to the increased procedural risks of coronary bypass surgery.

Hopefully, this commentary will serve as a call to arms (or needles) to my interventional colleagues. The unacceptably high rates of restenosis after balloon angioplasty in diabetic patients simply can no longer be overlooked and accepted. Rather than abandoning percutaneous intervention in these patients, what should be done? 1) It is apparent that rigid glycemic control must be studied. This therapy requires active collaboration with our endocrinology colleagues and should be tested after coronary bypass as well. 2) Aggressive adjunctive pharmacologic therapy with angiotensin-converting enzyme inhibitors, hypocholesteremic agents and oral glycoprotein receptor blocking agents is required. 3) The extent to which stent therapy has limited the stent restenosis/thrombosis risk in diabetic patients needs more careful prospective evaluation. In this regard, the cardiology community must actively support

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the efforts of replicating the BARI trial with modern revascularization techniques in diabetic patients. At the present time, if we recommend multivessel percutaneous intervention to our diabetic patients, aggressive risk factor modification, tight glycemic control and intensive routine noninvasive screening for asymptomatic restenosis must occur.

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